Searching for Improved Treatment Options for Human Internal Decontamination
A Nanoscale Approach

Michael D. Kaminski,[a,c] Carol J. Mertz,[c] Martha R. Finck,[c] Yumei Xie,[d] Haitao Chen,[d] Vivian Sullivan,[c] Sandra Guy,[b] Vincent Turitto,[d] and Axel J. Rosengart,[a,b]
[a]Co-Principal Investigator, [b]Pritzker School of Medicine, The University of Chicago, [c]Argonne National Laboratory, [d]Illinois Institute of Technology

Overall Research Goal

Develop, design, and demonstrate a novel, integrated system based on magnetic nanoparticles for selective, rapid removal of biological, chemical, and radioactive biohazards from humans.

Current Detoxification Methods and Limitations

Hemodialysis and Hemofiltration: Long procedure duration, extracorporeal circulation of large blood volumes, large-bore arterial access, non-selective substance removal, limited to hydrophilic substances with lower molecular weight

Plasmapheresis: Generally restricted to autoimmune diseases

Extracorporeal Immunoabsorption: Specific removal method but less effective, restricted to specific antibody-antigen interactions, requires circulation of large blood volumes

Direct Injection of Chelators and Antibodies ("Immunotherapy"): Incomplete antigen binding, relatively high antibody dosing; bound toxin can still be toxic or dissociate, leading to rebound intoxication

Overview of Proposed System

Injection

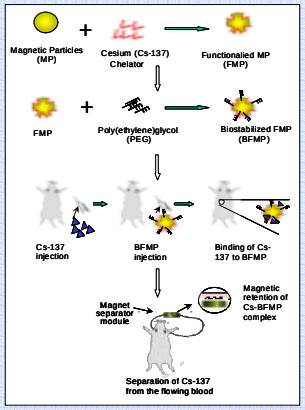
Magnetic nanospheres are developed that are biostabilized with polyethelyne glycol (PEG) to avoid rapid bioclearance. They are biodegradable and non-toxic and present a variety of specific toxin-binding receptors. These nanospheres are injected directly into the blood stream of exposed humans.

Chelation

Once injected, the nanospheres circulate freely through the blood stream, offering selective capture and sequestration of blood-borne toxins to the surface receptors.

Separation

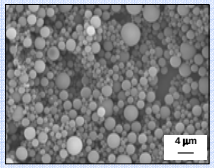
The magnetic separator device allows blood to pass through a closed-loop system containing tubular micro-channels designed to optimize blood flow and particle removal. Small magnets within the device trap the particle-toxin complexes at the tube walls and the detoxified blood is returned into the body. After the procedure, the toxin-bound particles can be flushed from the removable tubing and used as an analyte in further testing.



Advantages

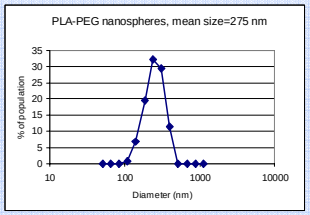
Therapeutically Superior: Active removal of biotoxins from exposed humans, not merely binding and passive secretion
Biocompatible: Non-toxic, biodegradable nanoparticles not removed will pose no harm to the subject.
Diverse: Already existing and newly designed antitoxins, antibodies, and ligands can be attached and multiple toxins can be removed ('cocktail' approach)
Repeatable: Chronic exposures or exposures with high tissue levels can be retreated
Compact: Total MNP-antitoxin injected expected to be <2 mg/kg body weight; injectants and magnetic separator device engineered as hand-held, single-use, pre-sterilized, self-applicable unit (in-field use, etc.)
Concentrates Toxin: Collected toxin provides a highly concentrated analyte for further identification.

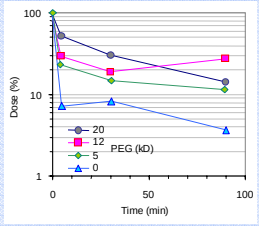
Magnetic Nanoparticles



Controlling Size

Oil-in-water emulsion (copolymer-magnetite-PLA-chloroform) has proven to be a poor technique. Membrane emulsification promises an improvement. The surfactant properties of PEG reduce emulsion size from 1-4 mm to 275 nm





Vascular Survival of PEGylated Nanospheres

Poloxamers

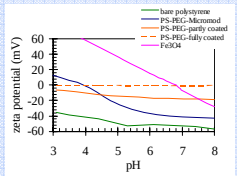
- PEG-PPG-PEG triblock polymers
- PPG: poly(propylene glycol) (hydrophobic)
- PEG: poly(ethylene glycol) (hydrophilic)

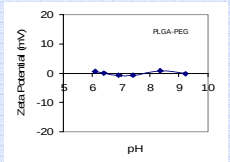
Attaching Receptors to PEG Terminus

The literature describes a coblock polymer synthesis with biotin end groups. These provide a direct method of attaching streptavidin or other receptors to the particle. This polymer is now being synthesized in our laboratory.

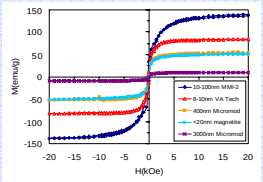
Surface Charge

A charged particle surface attracts plasma proteins; hence the surface charge needs to be near neutral (at pH 7). PEG neutralizes the surface and its flexible chains reduce the immune response.



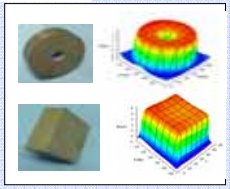


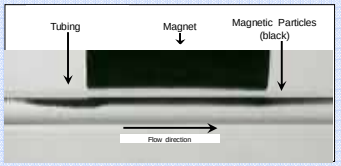
Magnetic Separation



High magnetization particles

Magnetic field gradients





In Vitro Separation of HRP

In vitro tests were conducted in both 0.9% saline and blood using 10 mg functionalized nanospheres per 40 mL fluid. The tests showed rapid kinetics and efficient removal (~70% in 15 min) of surrogate toxin (HRP) using magnetic nanoparticles.

Contact Time	15 min	60 min
Injected HRP (mg/mL)	0.38	0.38
Bound HRP (mg/mL)	0.27	0.27
Free HRP (mg/mL)	0.11	0.10
% HRP Bound	71.9	72.8

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